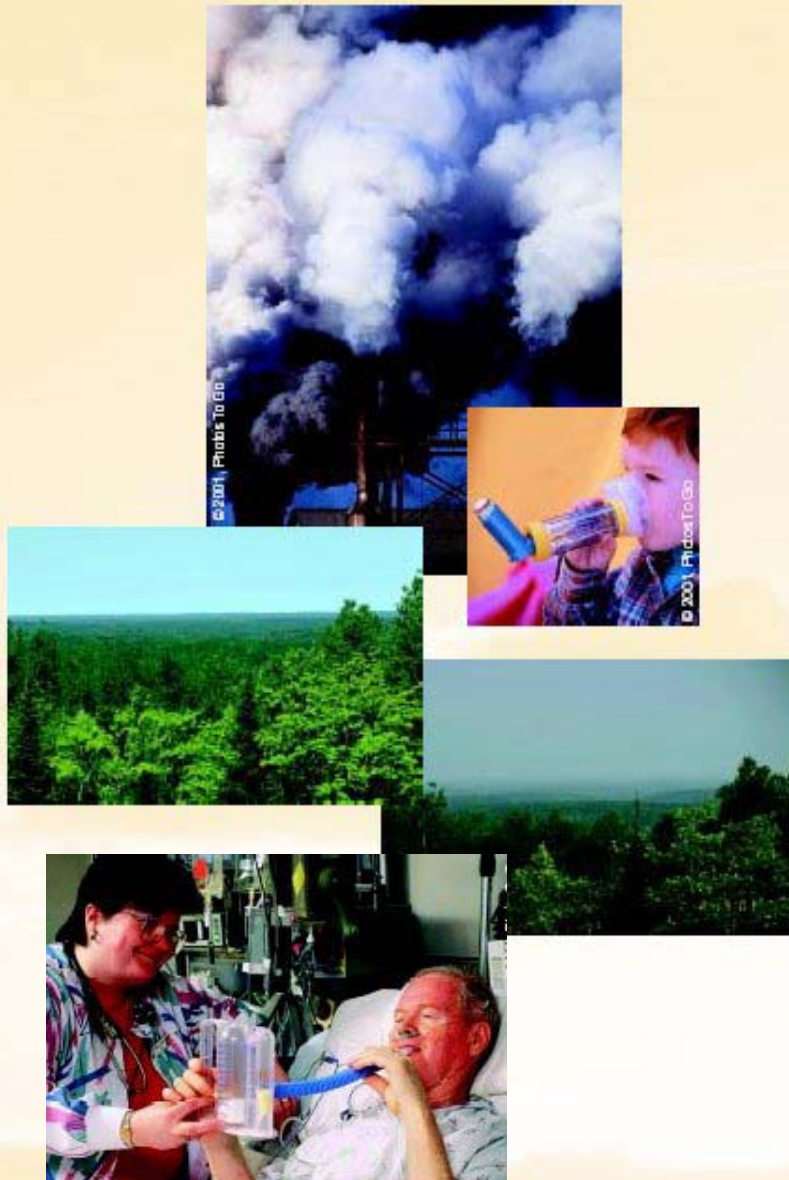


# Evidence for PM Sources and Types Causing Premature Mortality



**Dan Costa, Sc.D.**

KL Dreher, MI Gilmour UP  
Kodavanti, W Linak, A. Miller

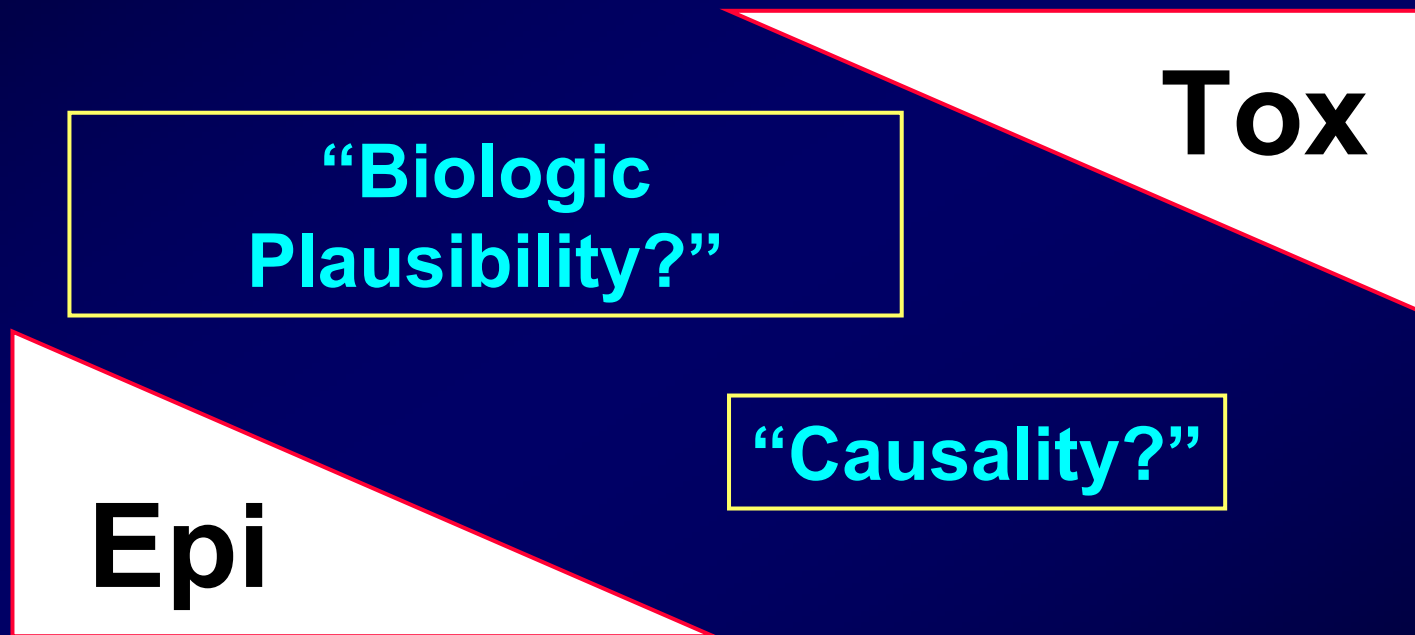
**ETD / NHEERL / NRMRL / ORD**

costa.dan @epa.gov



# *What is it About PM That Leads to Health Effects?*

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- Exposure Issues
- Susceptibility
- Mechanisms of Injury

# Ambient PM: Potentially Hazardous Characteristics

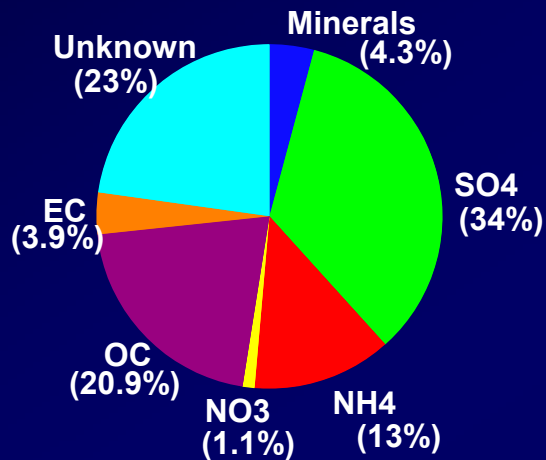
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- ◆ Particle Acidity ( $\text{H}^+$ ;  $\text{SO}_4^{=}$ ;  $\text{NO}_3^-$ ;  $\text{NH}_4^+$ )
- ◆ Physical Properties (size; number; surface area)
- ◆ Organic Components (PAHs; quinones; peroxides)
- ◆ Inorganic Components (silicates; salts; oxides; metals)
- ◆ Biological Components (allergens; endotoxin)
- ◆ Co-pollutant Interactions w/  $\text{O}_3$ ;  $\text{SO}_x$ ;  $\text{NO}_x$ ; CO

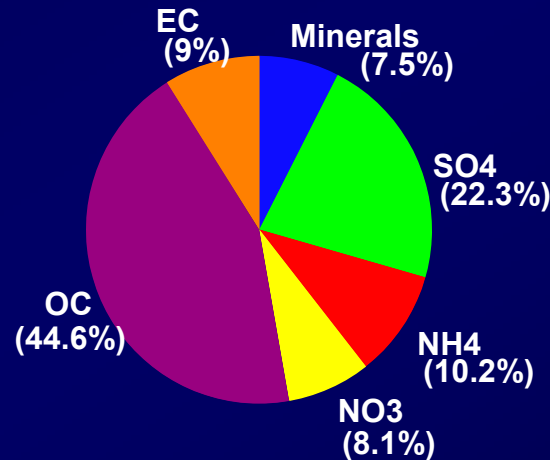
# The Challenge to Toxicologists

- In search of relatively rare events at low doses
- Ambient PM is a *physicochemically complex & dynamic mixture* of constituents derived from 1° and 2° sources

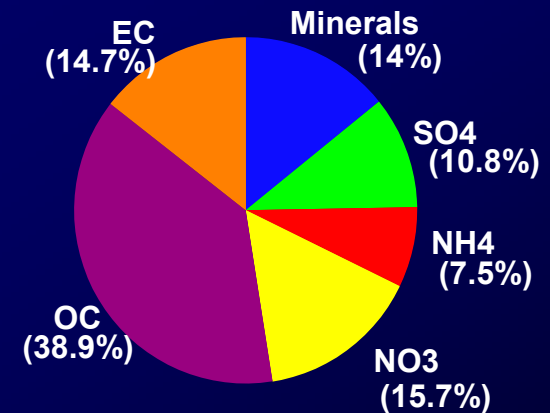
## Eastern US



## Central US



## Western US



**Co-Pollutants:** SO<sub>2</sub> NO<sub>2</sub> NH<sub>3</sub> O<sub>3</sub> VOCs Biologics

Particle Acidity

# Criteria to Evaluate Toxicology Approaches to PM Plausibility Theories Regarding Attributes

---

- Are there environmental **sources**?
- Is there evidence of **personal exposure**?
- Is there sufficient **toxic potential** of the putative property?
- Can **toxic mechanisms** be **extrapolated** to the human exposure situation?
- Is there **coherence** with the epidemiology?
  - Consistency
  - Exposure-Response
- Does the theory hold across **diverse** exposures?

# A Role for 'Acid' Aerosols?

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## $\text{SO}_4^-$ Aerosols

---

### Epi (mortality / morbidity):

- Fine PM assoc: mortality, asthma hosp.

### Lung Function:

- Healthy Adults: no effect at  $<1 \text{ mg/m}^3$
- Asthmatics: effects at  $\sim 75 \text{ ug/m}^3$
- Guinea pigs: effects at  $\sim 200 \text{ ug/m}^3$

### Host Defense:

- Altered mucociliary clearance  $0.1 - 1 \text{ mg/m}^3$
- Altered AM function  $< 1 \text{ mg/m}^3$

### Airway Morphology:

- acute / chronic  $>> 1 \text{ mg/m}^3$ :  
alveolitis, edema, epithelial damage
- chronic  $0.125 - 0.5 \text{ mg/m}^3$ :  
↑ bronchial secretory cells ( $\propto \text{O}_3$ )

## $\text{NO}_3^-$ Aerosols

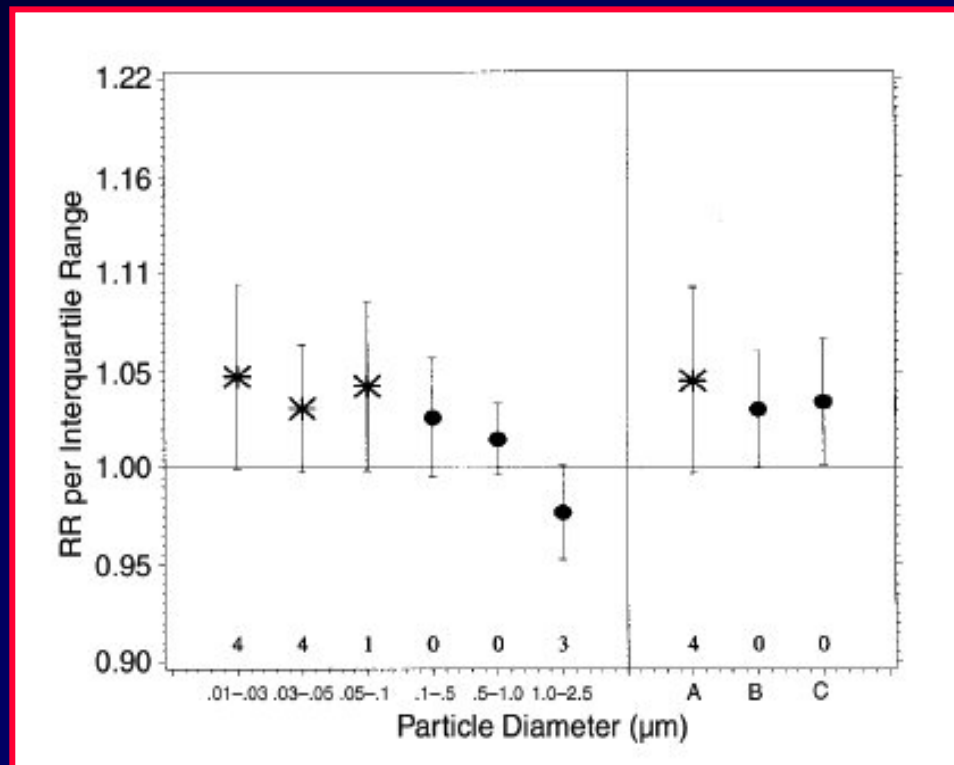
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### Health Effects:

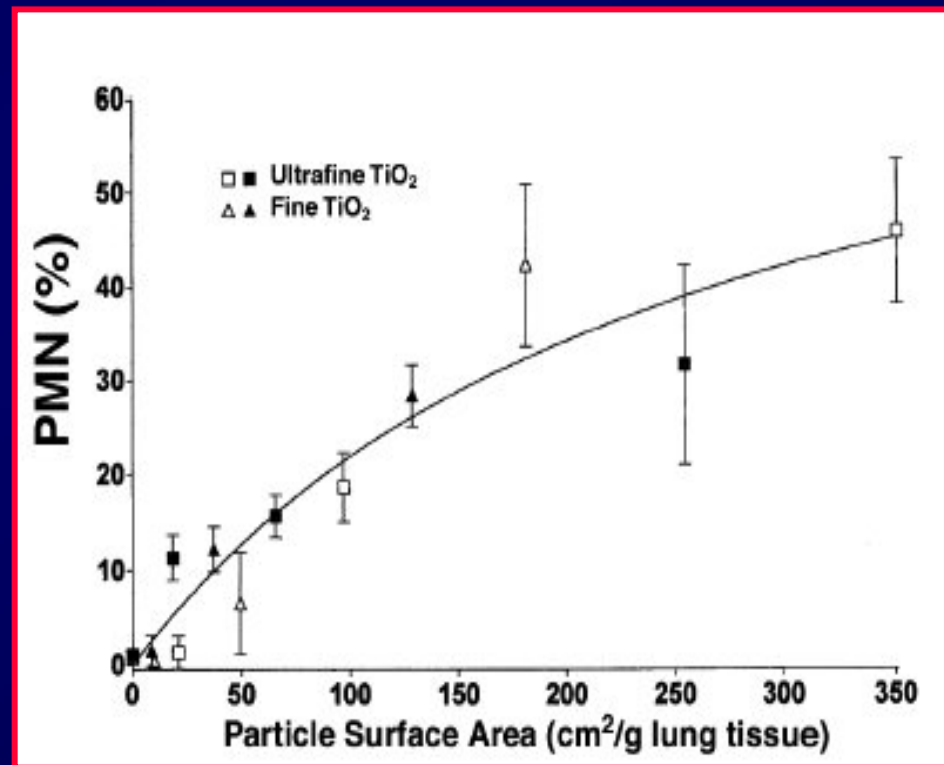
- Not as widely studied
- Generally minimal acutely
- South Calif. kids cohort?

# A Role for Physical Properties?

## Influence of Number and/or Surface Area on PM Toxicity



Wichmann et al., *HEI Report 98:58*, 2000

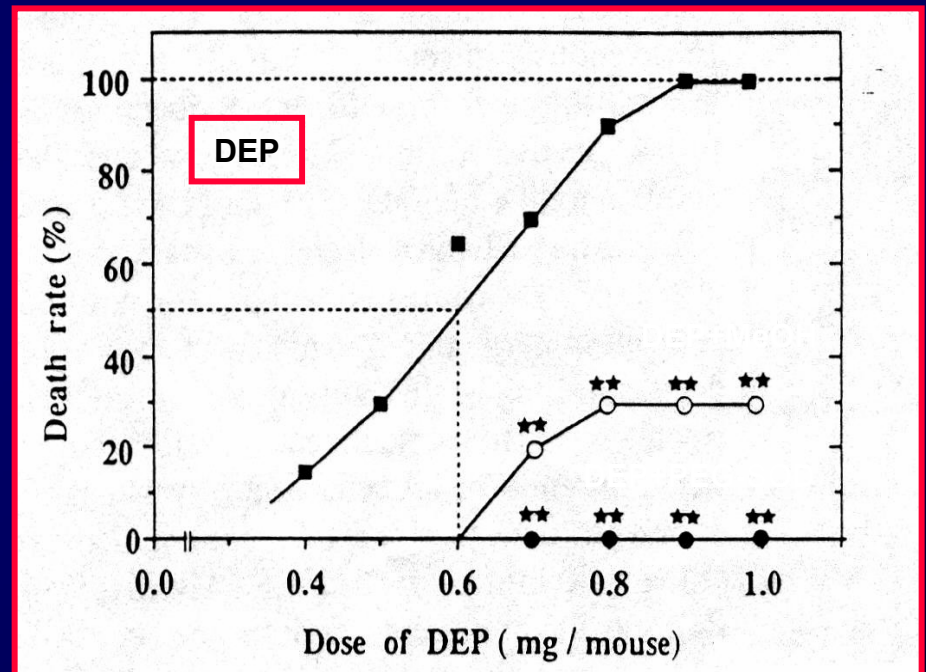


Oberdorster et al., *HEI Report 96:22*, 2000

# A Role for Organic Constituents?

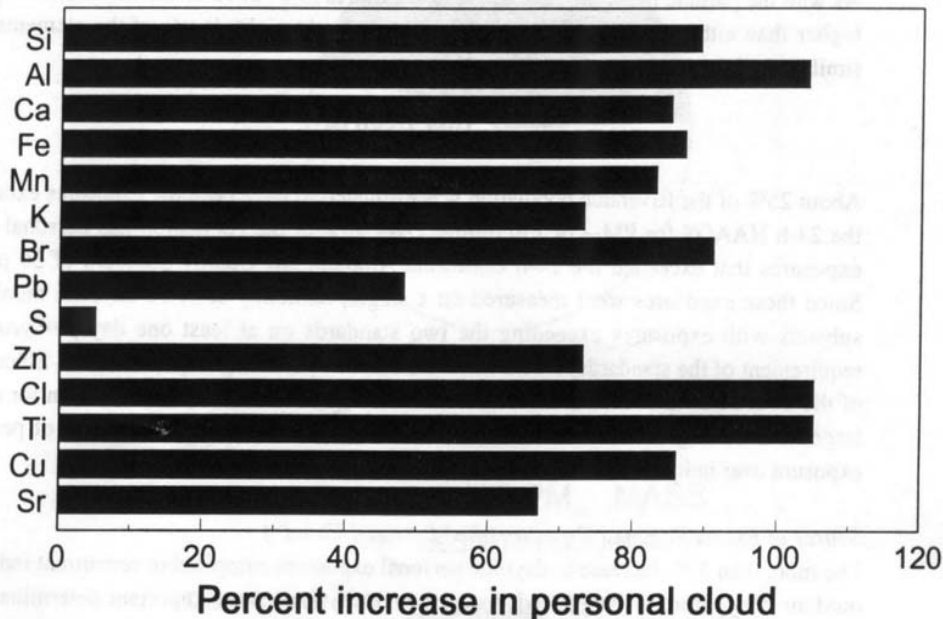
- Cancer Risk?
  - (Pope et al, 2002)
- Role of organics (quinones, nitroaromatics etc.) in oxidant production
  - (Sagai et al., 1997; Nel et al., 2001 )
- Induction of  $T_{H2}$  cytokine profile & eosinophilic inflammation in airways & mediastinal lymph nodes
  - (Lovik et al, 1997, Sagai et al, 1996, Miyabara et al, 1998 Tanako et al, 1997; Diaz-Sanchez et al., 1997)

## Oxidants & Mortality



Sagai et al, *Free Rad. Biol. & Med.* 1993.

***How would these criteria  
apply in the case of PM-  
associated metals?***



## Personal Cloud Exposure to Metals

*Ozkaynak et al., JEAAE, 1996*

## Metals Accumulate in Human Lungs

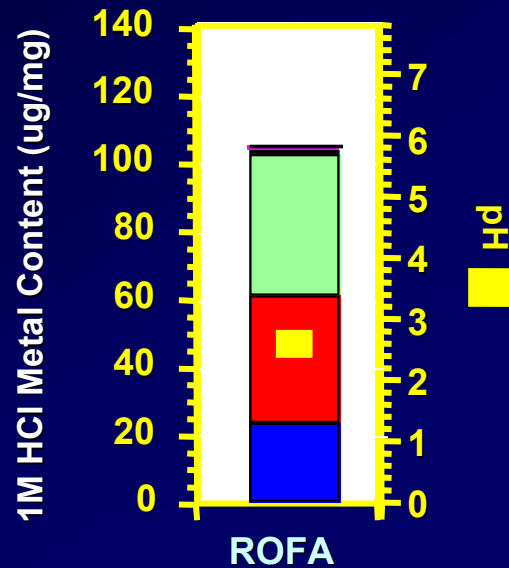
*Fortuol et al., EHP, 1996*

**Table 2.** Mean concentrations of metals in lung tissue from the 1980s and the 1950s

Element	Mean $\pm$ SD (mg/g dry weight)	
	1980s ( $n = 84$ )	1950s ( $n = 69$ )
Cadmium	25.6 $\pm$ 6.5	1.2 $\pm$ 0.37
Cobalt	37.2 $\pm$ 8.67	3 $\pm$ 0.97
Copper	44.8 $\pm$ 15.7	10 $\pm$ 2.97
Nickel	57.6 $\pm$ 9.3	3 $\pm$ 0.96
Lead	134.3 $\pm$ 26.7	12 $\pm$ 4.97

# A Role for Metals in PM Health Effects: Primary Combustion PM - ROFA

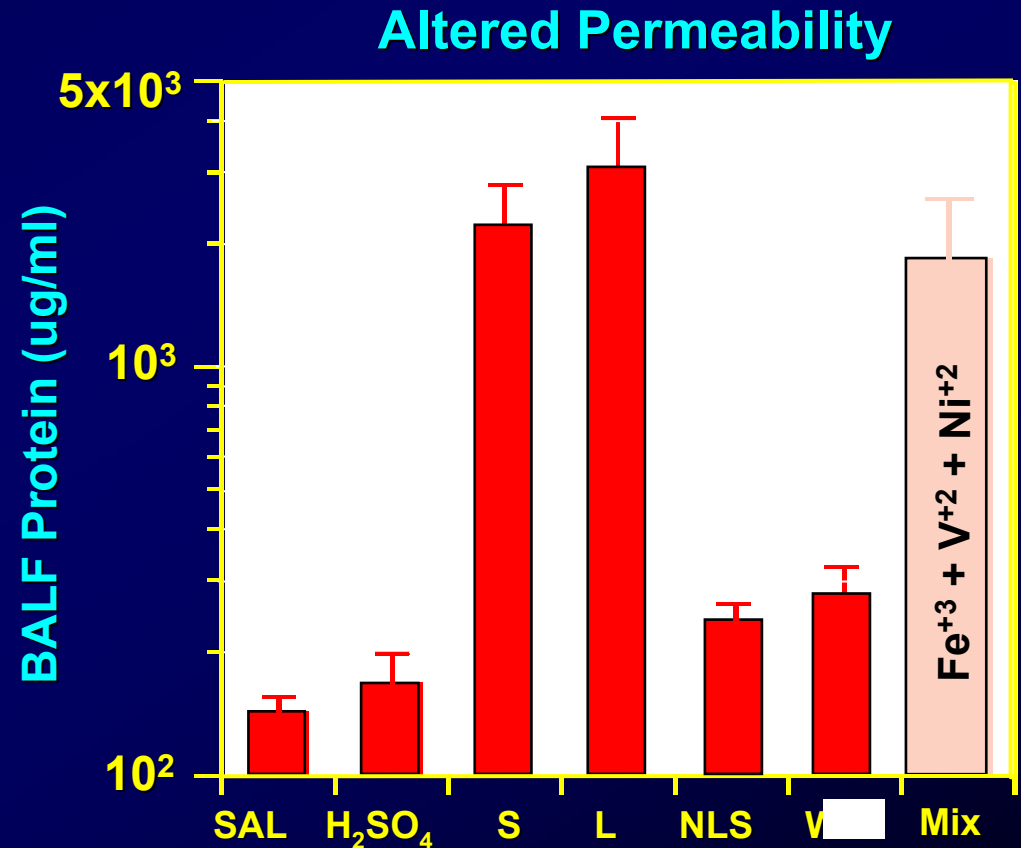
Cu Zn V Ni Fe



MMAD Size: 1.95  $\mu\text{m}$   
% OC: 1  
% EC: 0

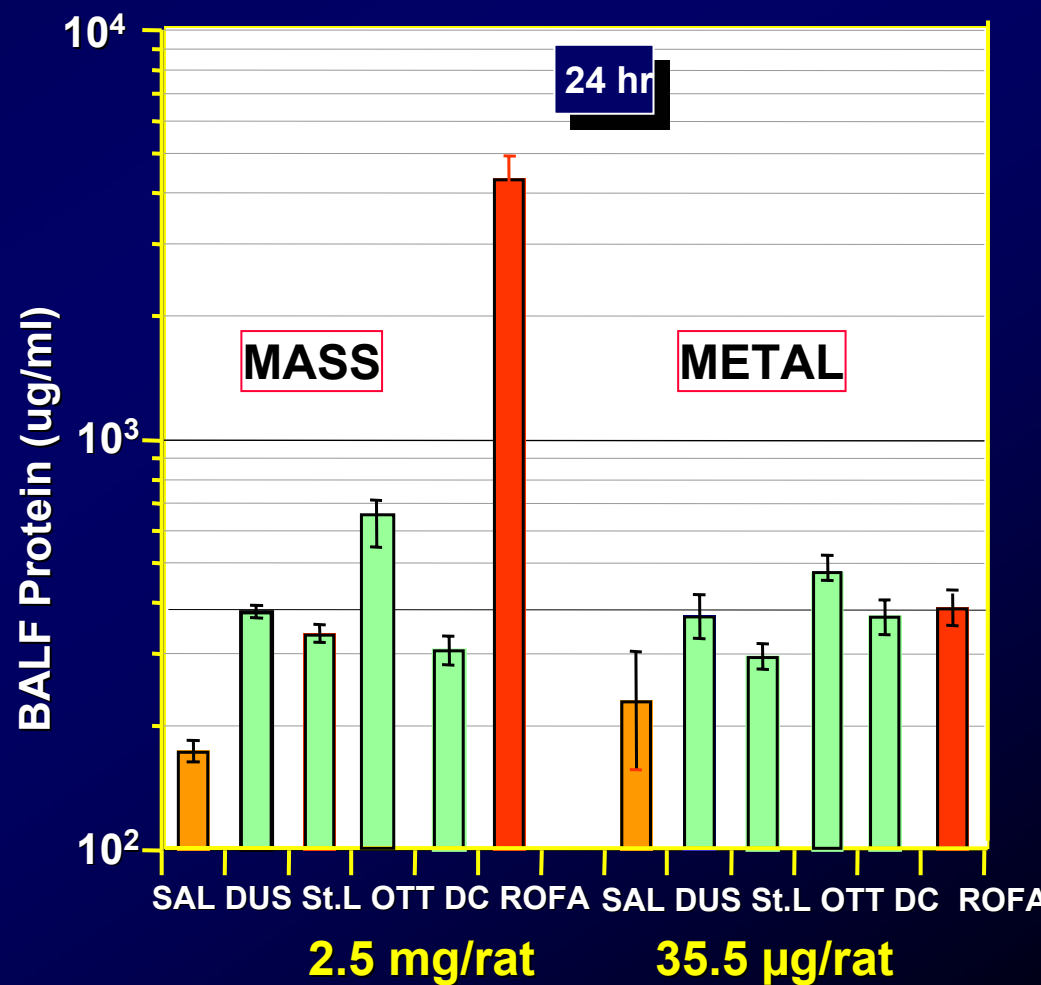
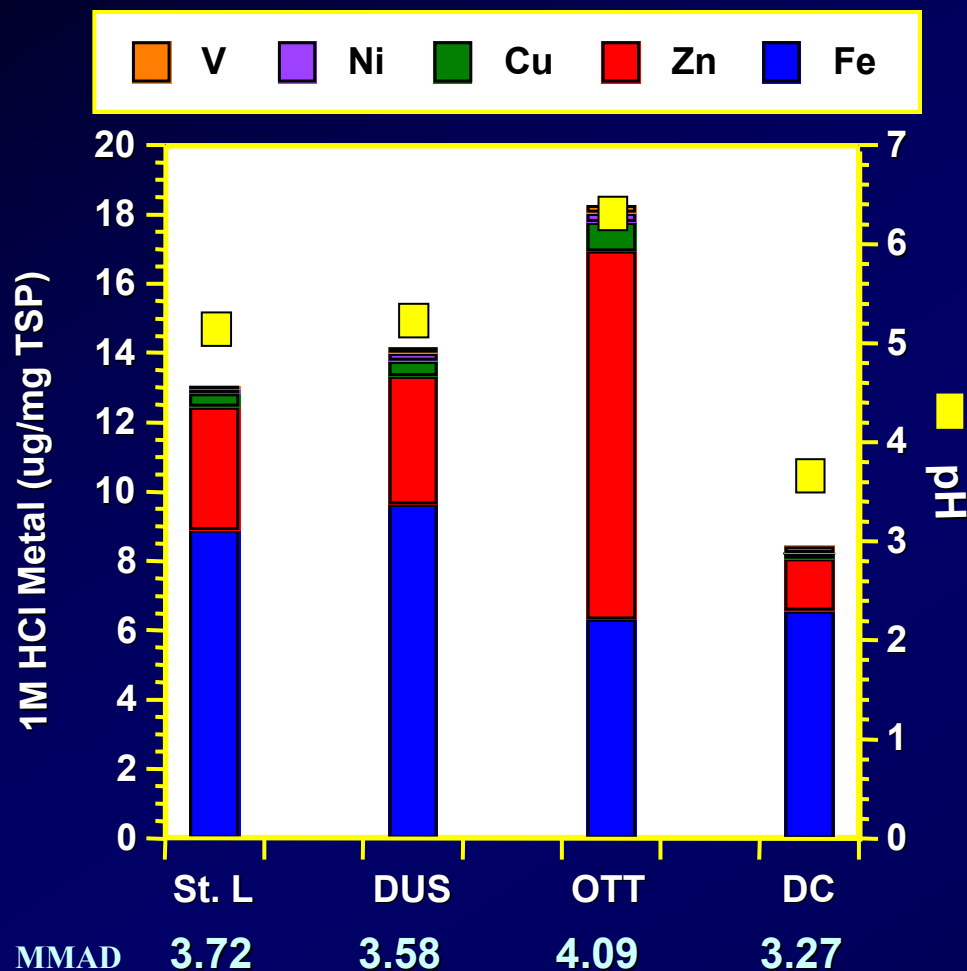
Sulfate: 560  $\mu\text{g/mg}$

Water Soluble Metal: 88%



*Dreher et al., 1997*  
*Gavett et al., 1997*

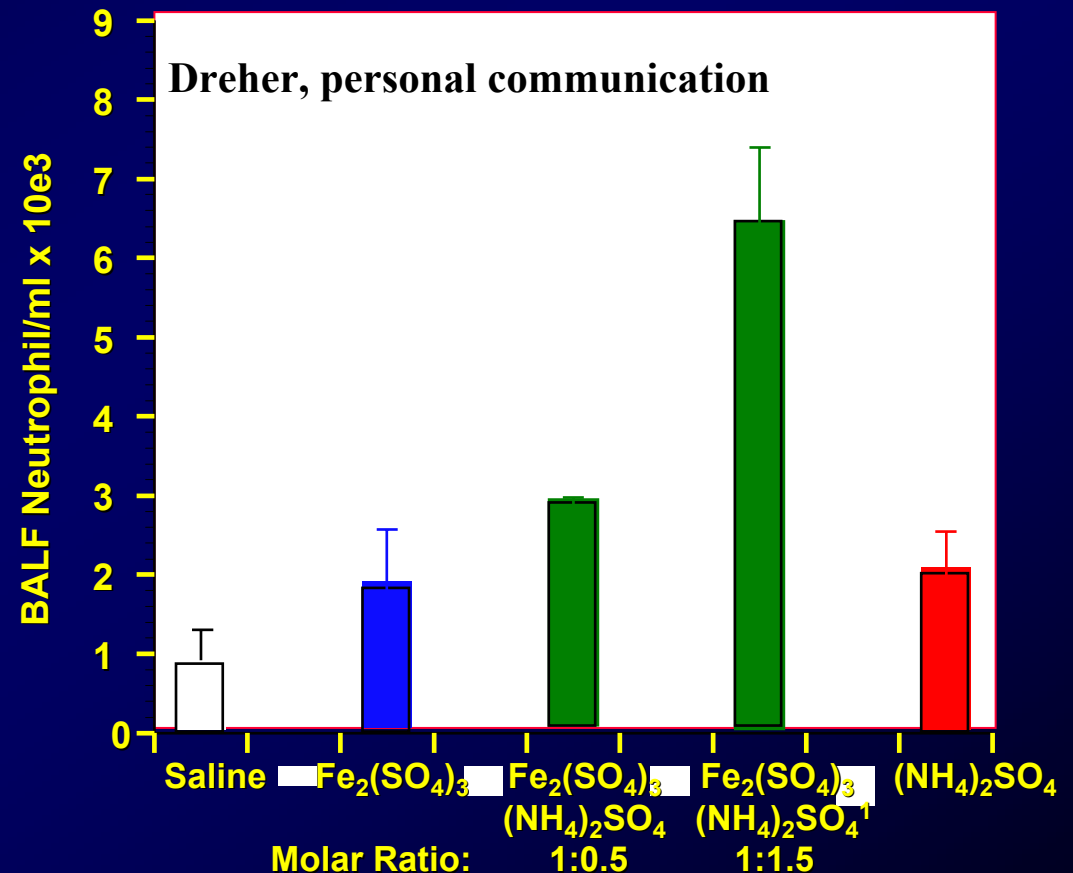
# A Role for Metals: Ambient PM



# Interactive Roles for Acid Sulfates?

- Historic tox data base of PM + SO<sub>2</sub>  
— (Amdur et al. '60's – '80's)
- Epi data shows occasional co-pollutants – NO<sub>2</sub>, SO<sub>2</sub>, CO, O<sub>3</sub>  
— (Burnett et al, 1998; Gold et al., 1999; Wichmann et al., 2000)

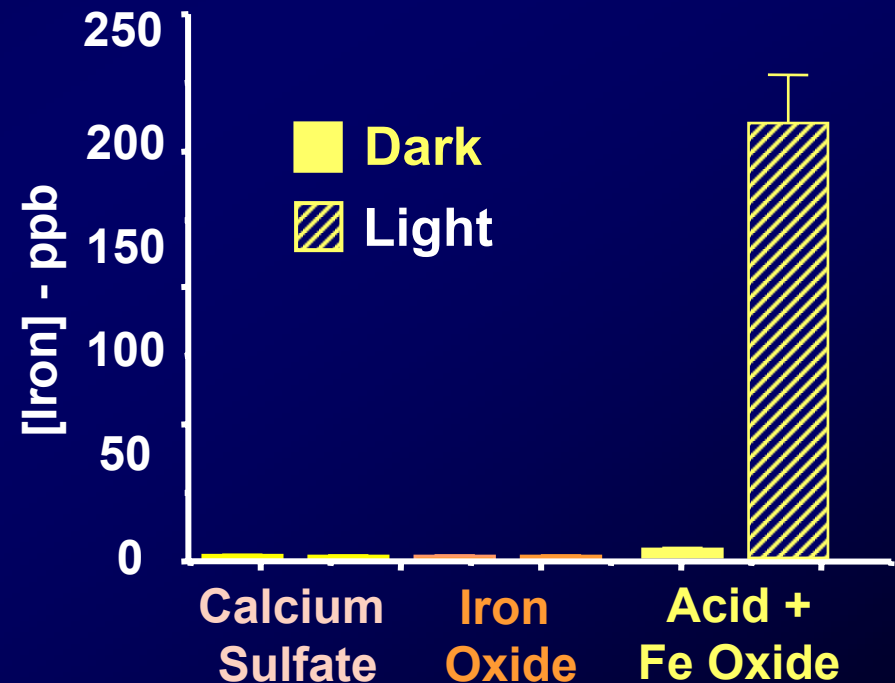
## Pulmonary Inflammation



# 'Acids' What Now?

- Sulfates (nitrates?) – surrogates or culprits (déjà vu); maybe it depends on co-constituents
- May act as irritants to alter autonomic control of cardiac function as well as PFT's in some individuals
- Complex and unclear 1° and 2° roles of acids as part of the PM complex

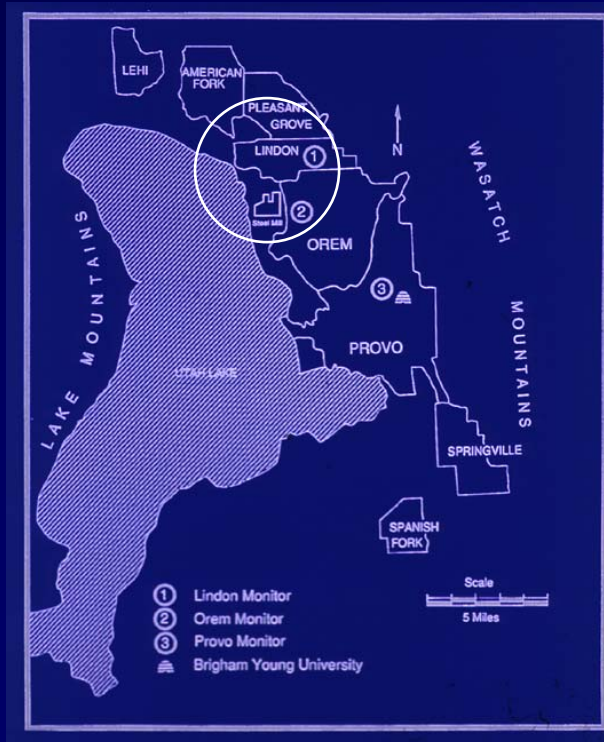
## Complex Acid Photochemistry May Help Mobilize Metals from PM



*Ghio et al., 1999*

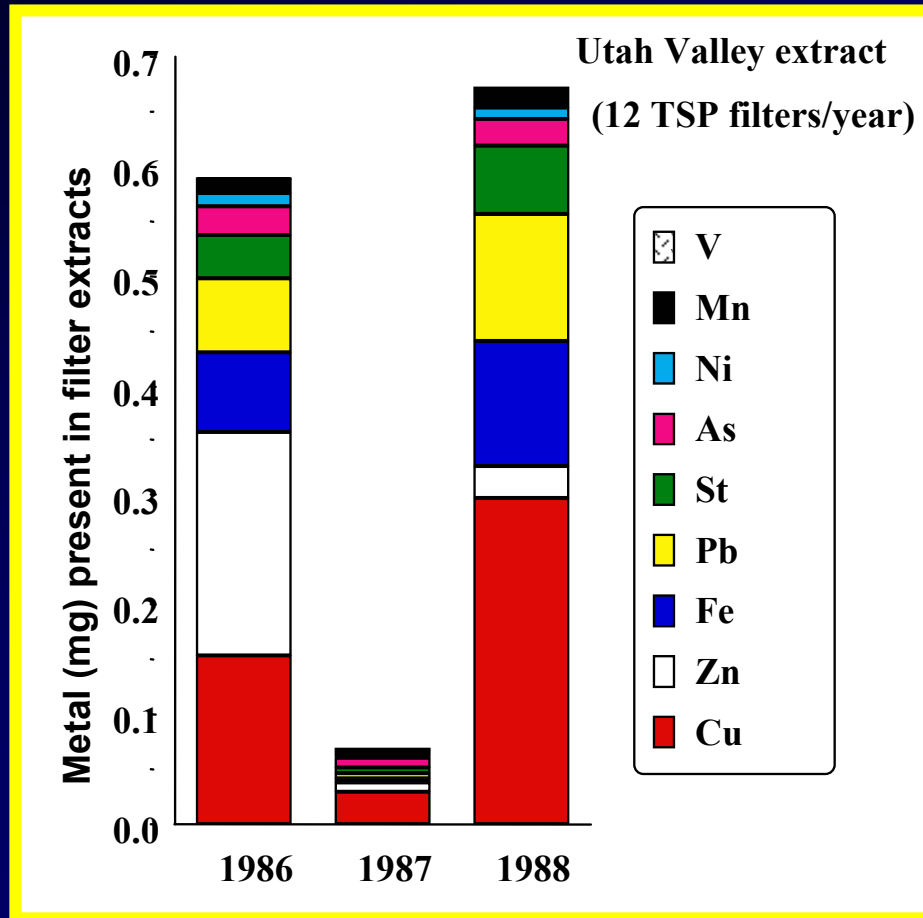
# Sources of PM<sub>10</sub> Pollution in the Utah Valley (1985-87)

Geneva Steel	82% of industrial emissions when operating 47- 80% of total emissions
Wood Burning	16%
Road Dust	11%
Diesel Fuel	7%
Oil Combustion	7%

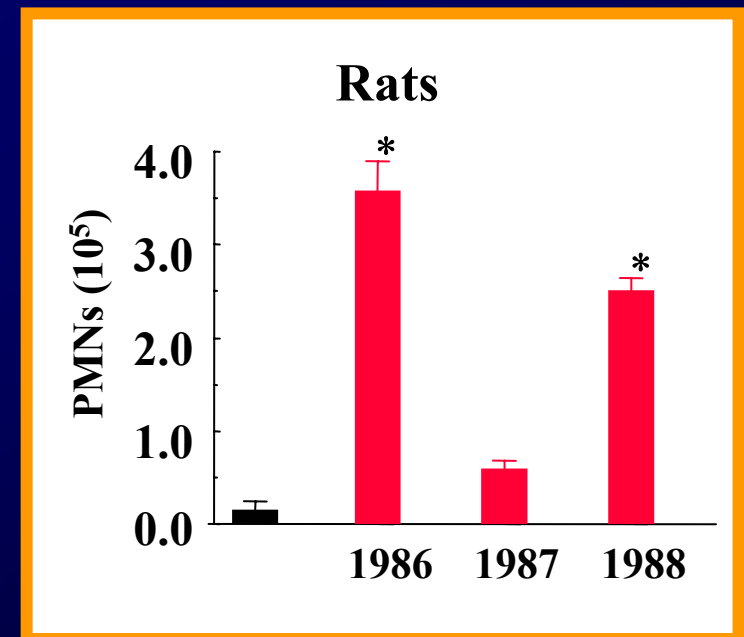
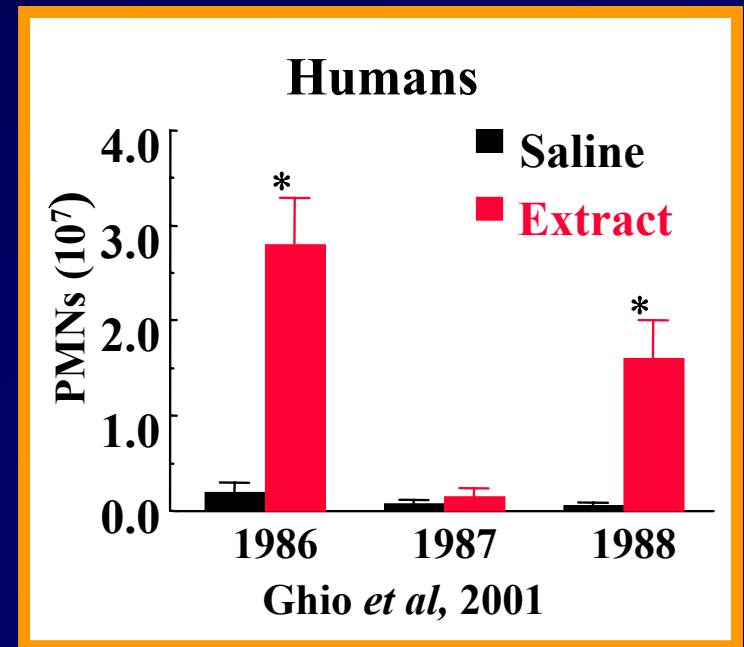


# Real-World Role for Metals?

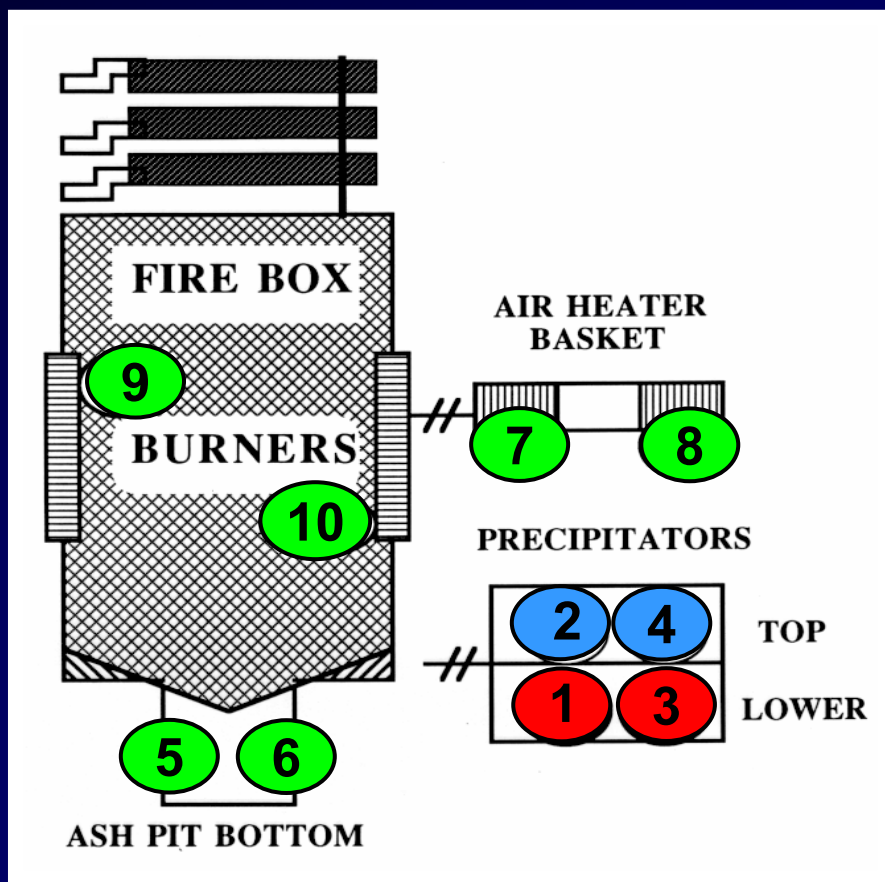
## Utah Valley filter extract metal analysis



Dye *et al*, EHP 2001



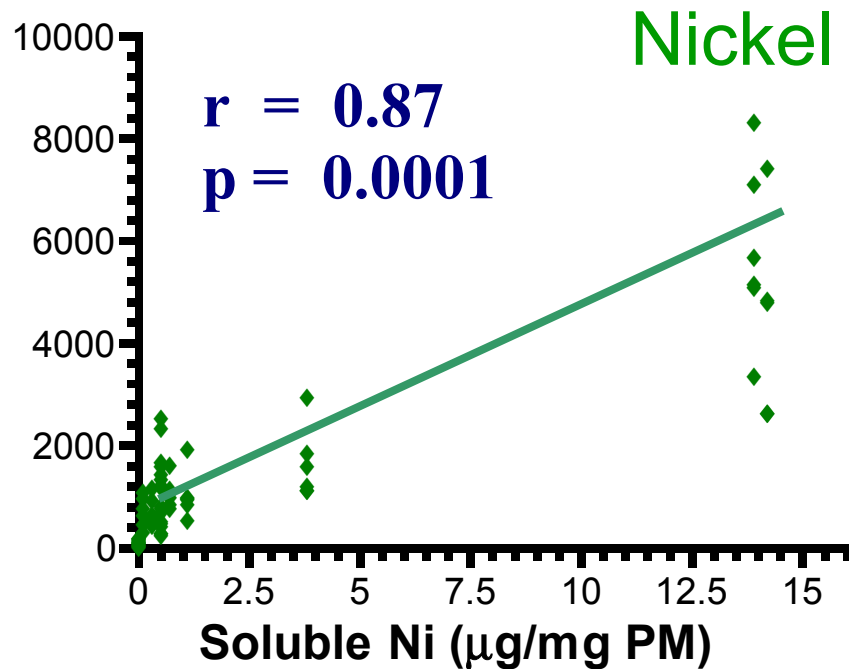
# How does oil fly ash with different metal composition affect toxicity?



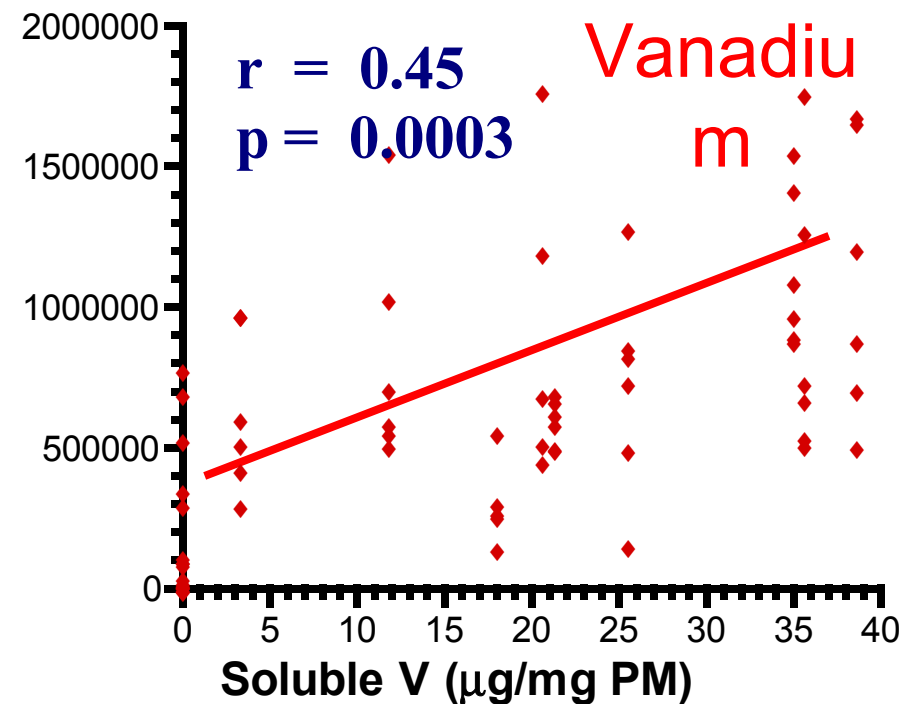
- Ten oil fly ash samples (boiler)
- Determine [metal] total and soluble
  - **Low**, **Moderate (V)**, **High (Ni +V)**
- Establish relative toxicity at 24 hr
- Use multiple regression and correlation analysis

# Associations of Nickel and Vanadium with lung injury and inflammation

## BAL Protein



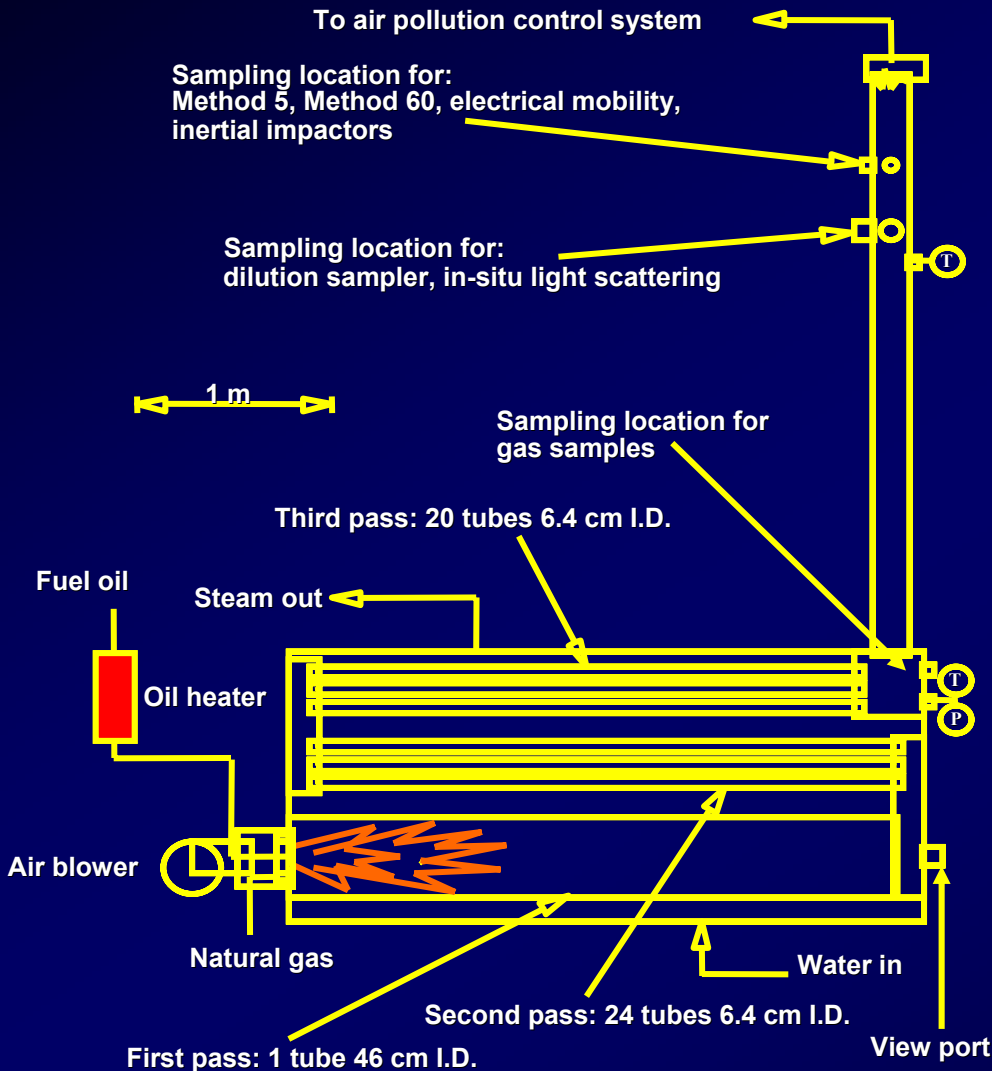
## BAL PMNs



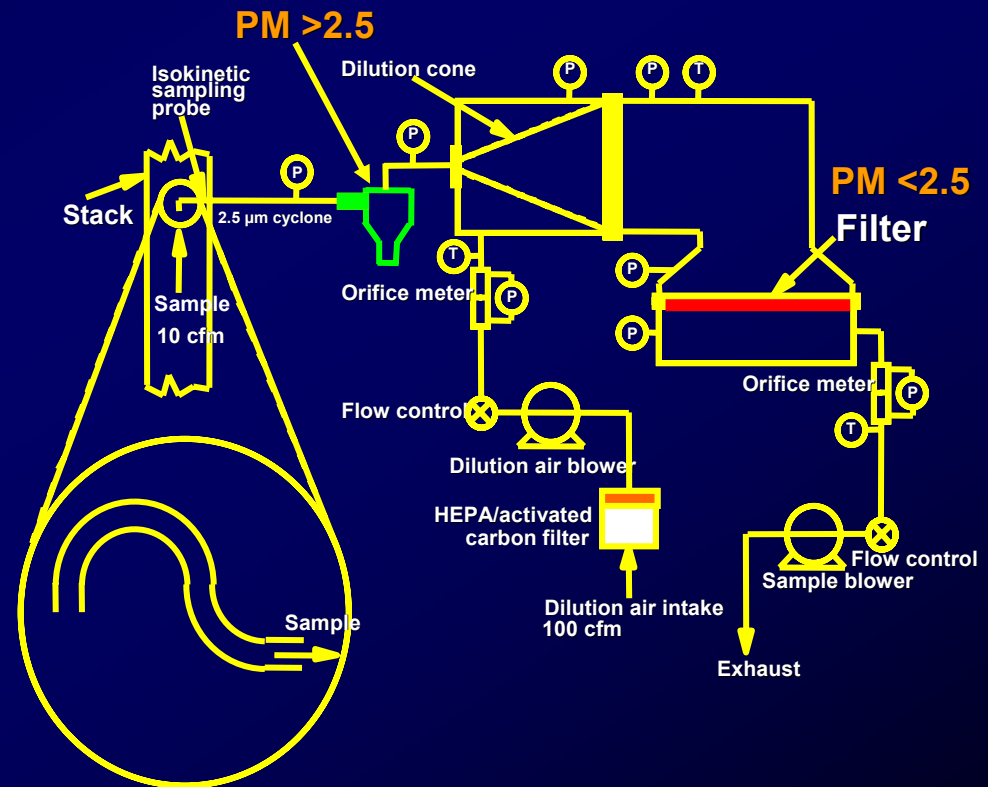
***Are the range of sizes of  
combustion PM of oil of  
similarly toxicity?***

# North American Package Boiler

## BOILER DIAGRAM

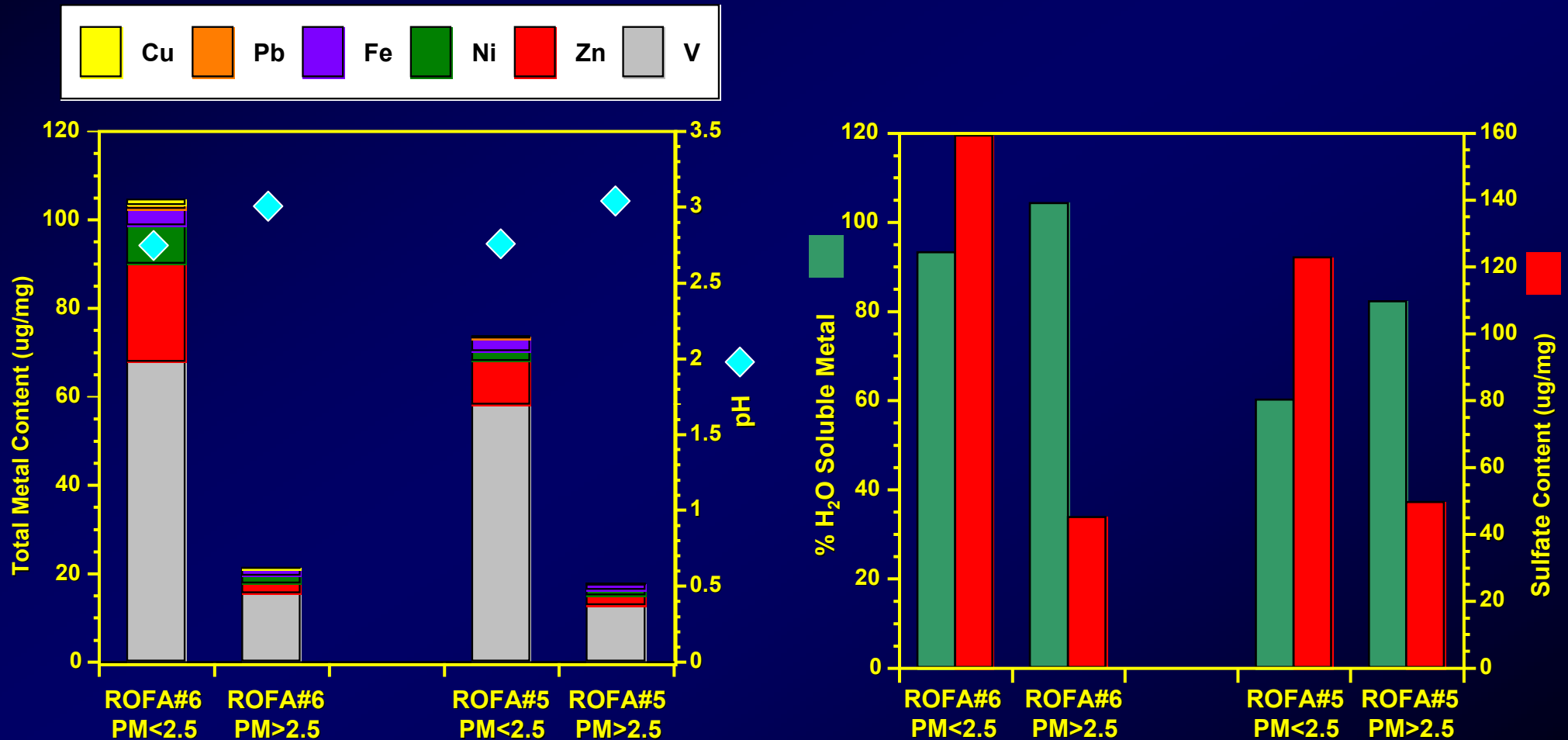


## PARTICLE COLLECTION



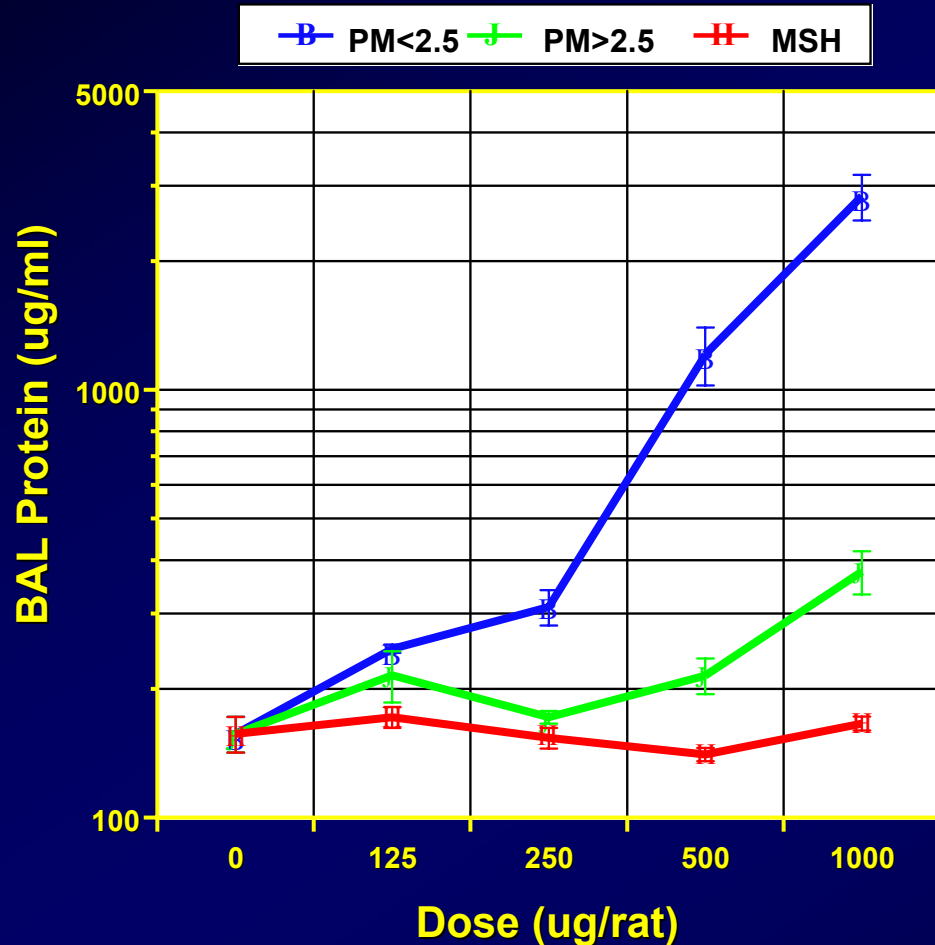
North American Model 61121-2.5H6-A65, three pass, fire-tube package boiler (NAPB).

# PHYSICOCHEMICAL ANALYSIS OF FUGITIVE (PM<2.5) AND RETAINED (PM>2.5) HS#6 AND BL#5H ROFAs

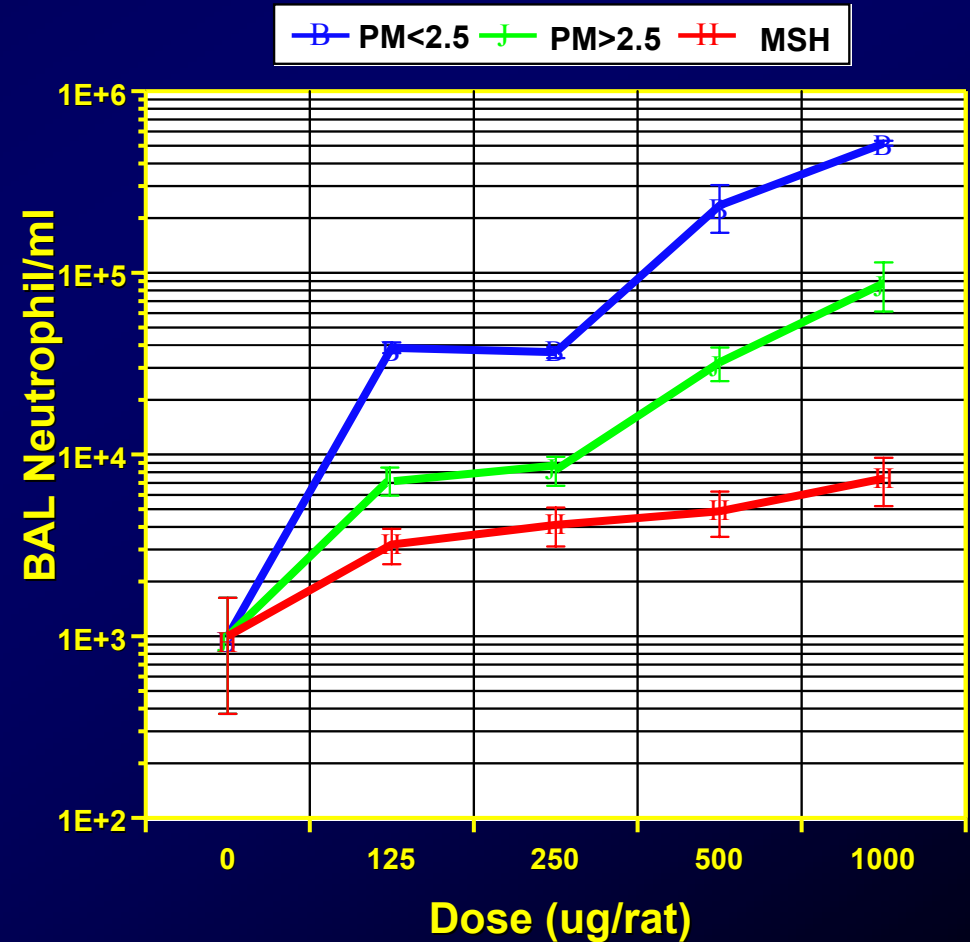


# PULMONARY TOXICITY OF FUGITIVE (PM<2.5) AND RETAINED (PM>2.5) ROFA HS#6

## Permeability

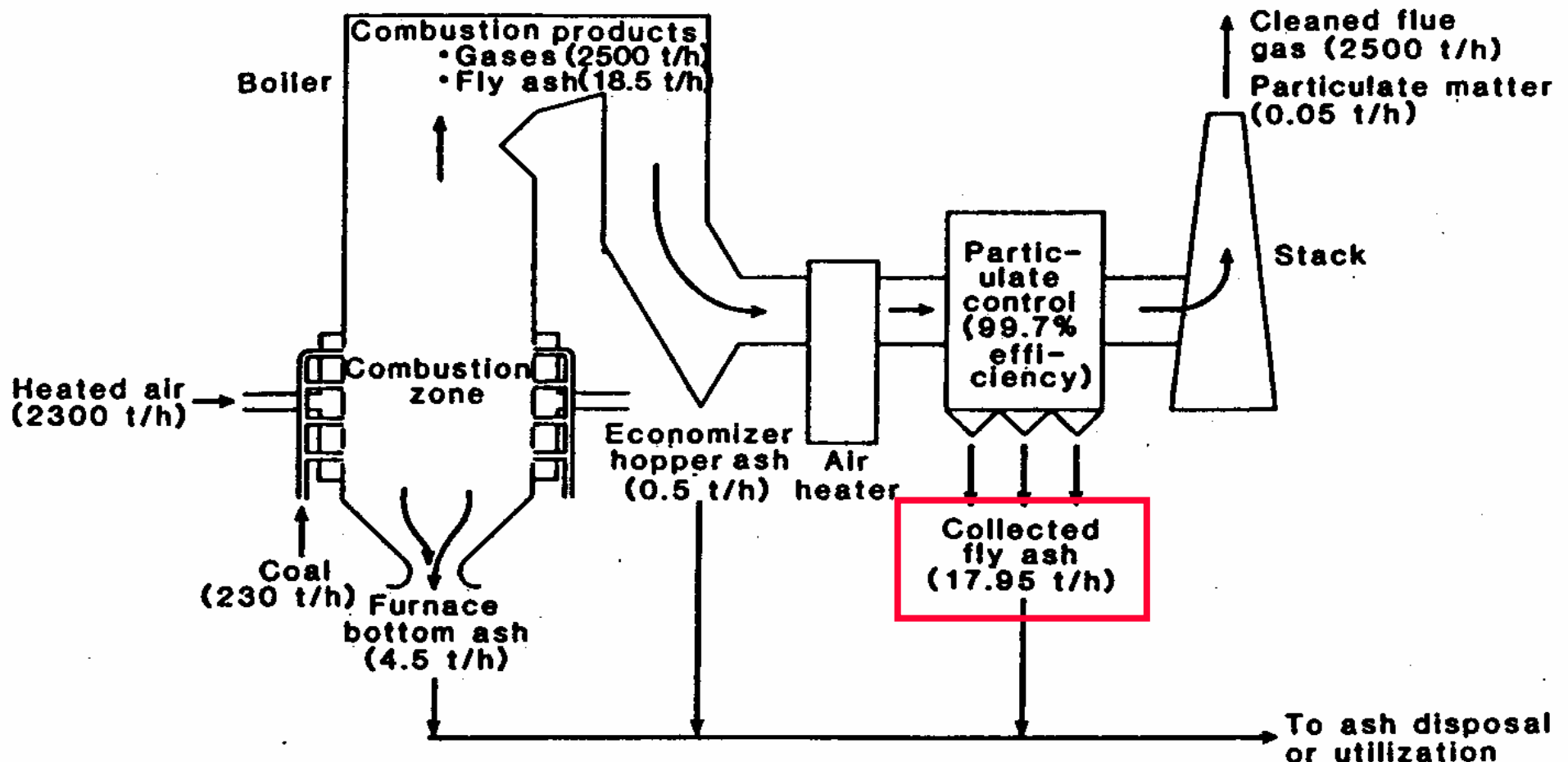


## Inflammation

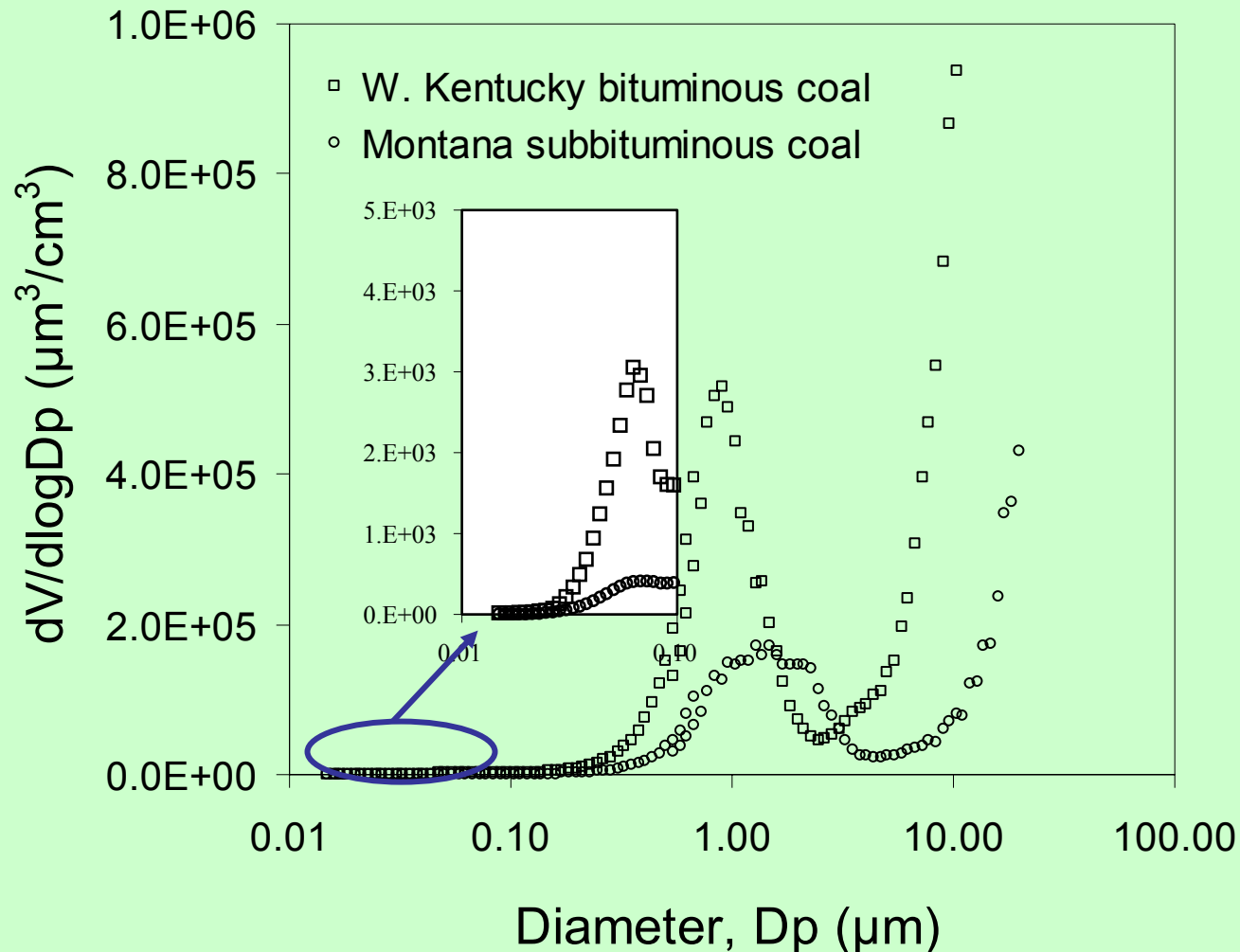


***What about coal  
emission PM?***

# Typical coal combustor system used in both large scale (power production) and small scale (experimental) situations

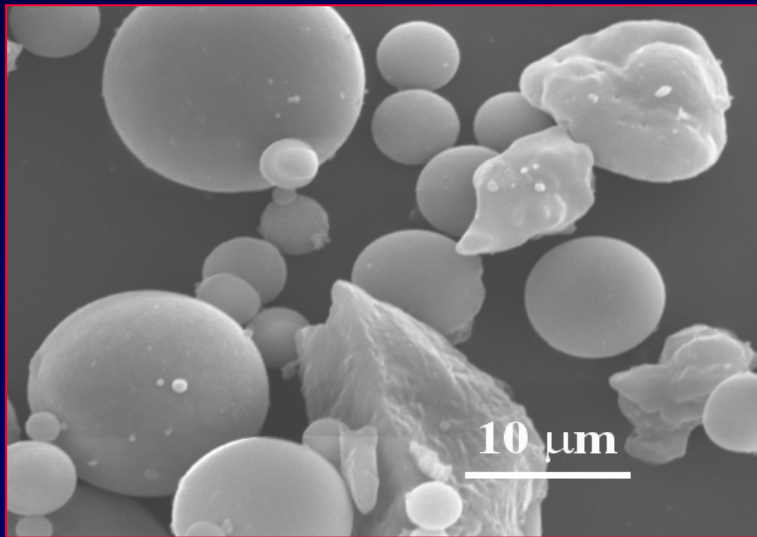


# Size distribution of two types of coal after combustion in a pilot scale utility boiler

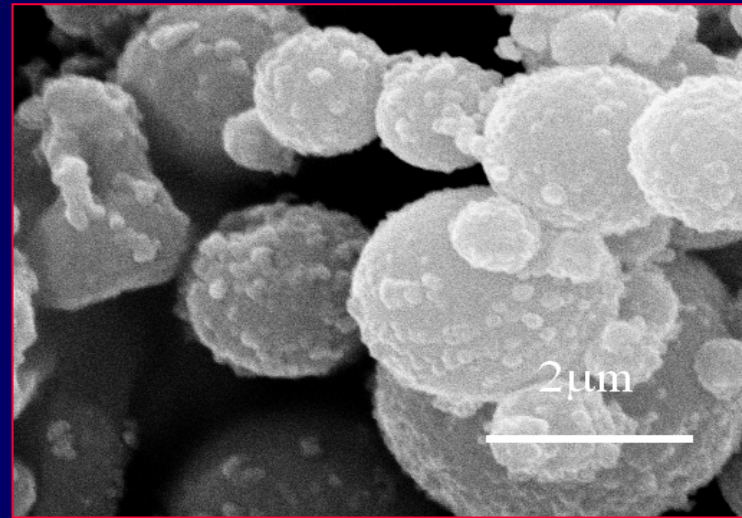


# Electron micrographs of three different fractions of Montana coal fly ash

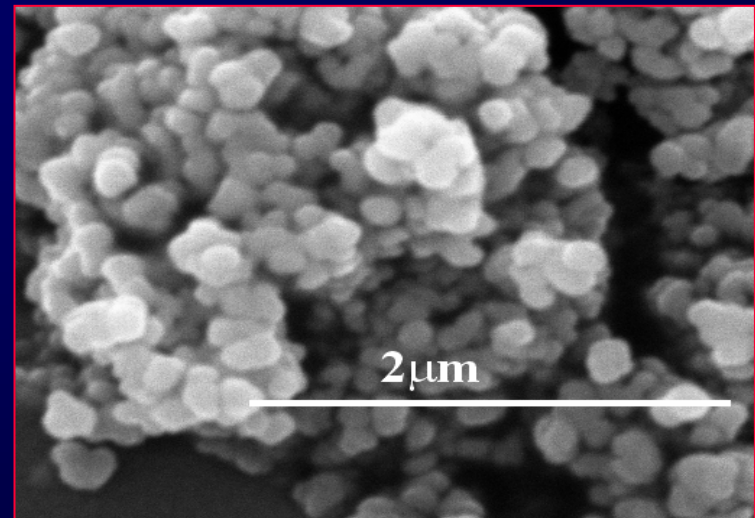
Coarse



Fine



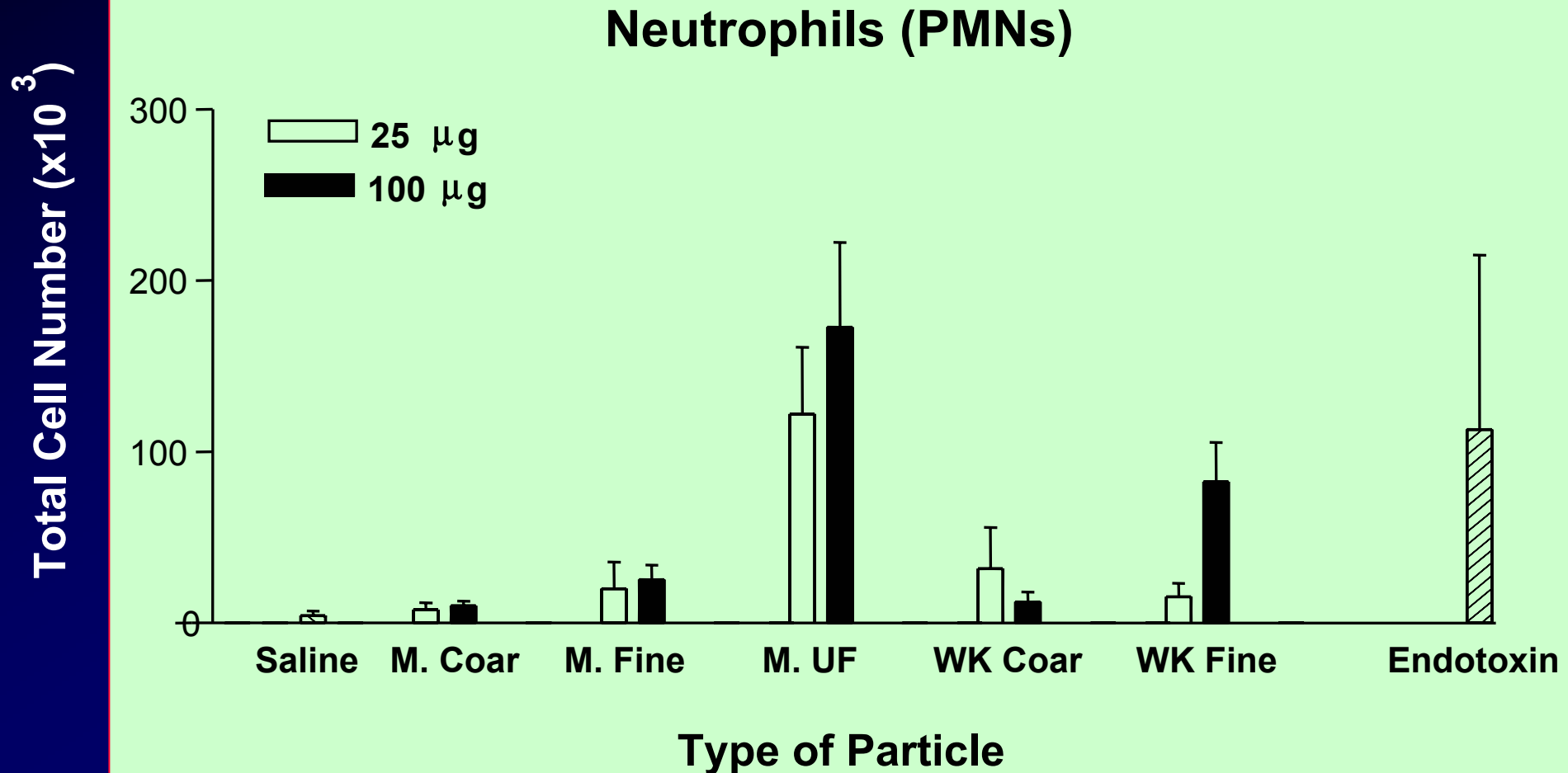
Ultrafine



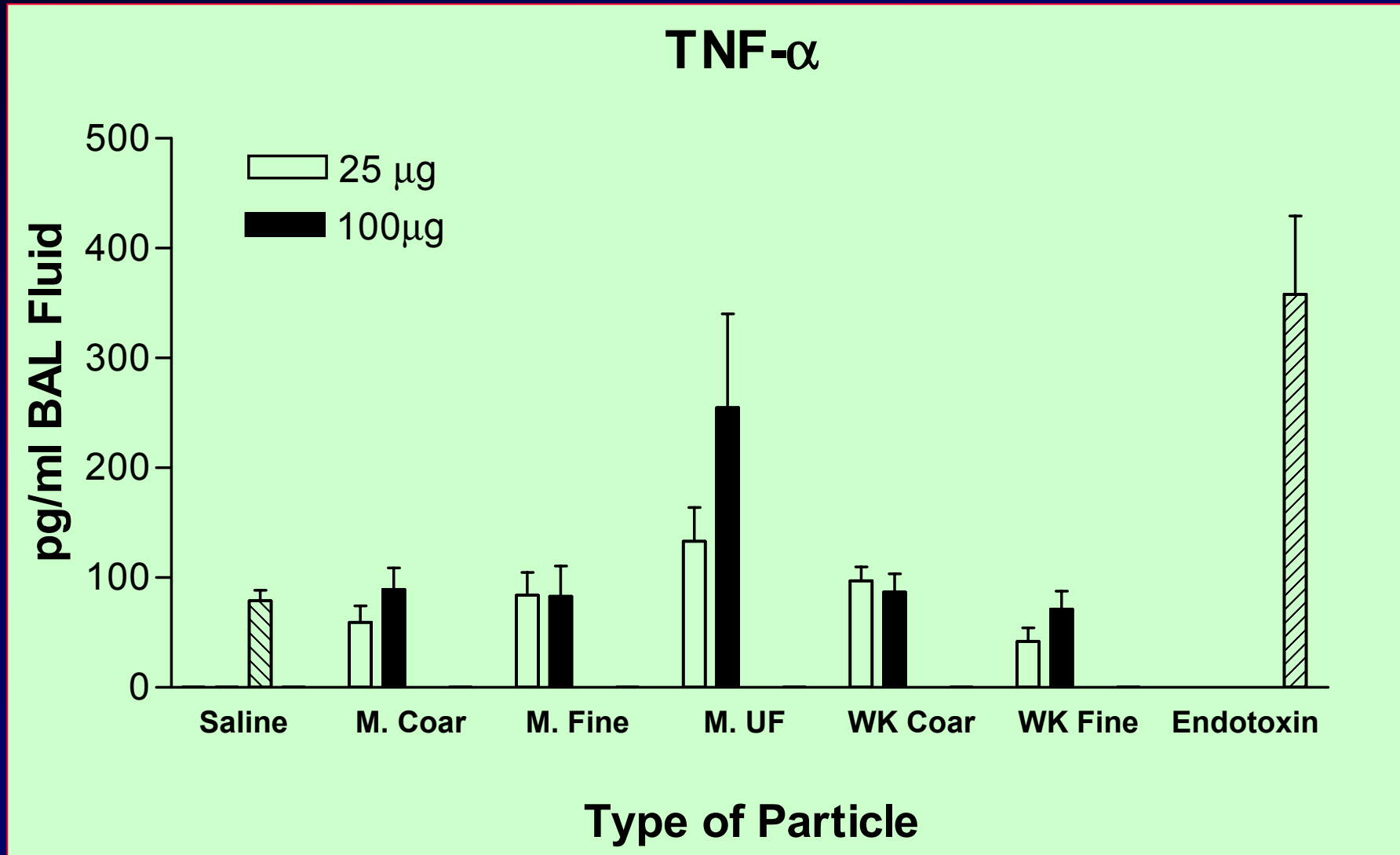
# Elemental analysis of ultrafine, fine and coarse coal fly ash

Element µg/g ash	MT UF	MT <2.5µm	MT>2.5 µm
Si	28,500	156,742	222,875
Al	93,780	103,979	108,800
Ca	82,900	89,858	115,175
Fe	6,920	53,929	30,350
S	39,400	7070	9,130
Mg	14,600	27,721	31,300
Ti	1845	6353	6180
K	1155	9358	5660
Cl	659	1264	1460
Ba	16200	2298	1843
P	10530	1080	979
Sr	7480	3426	3858
V	712	208	108
Ni	330	347	
Nb	910	176	22
Mn	487	1048	907
Cd	1620	463	
Se	565	136	
Ga	460	83	27
Cu	420	320	77
<hr/>			
Elements %	22.5	47	54
Oxygen %	16.5	44.5	45
Carbon %	unknown	0.4	0.5

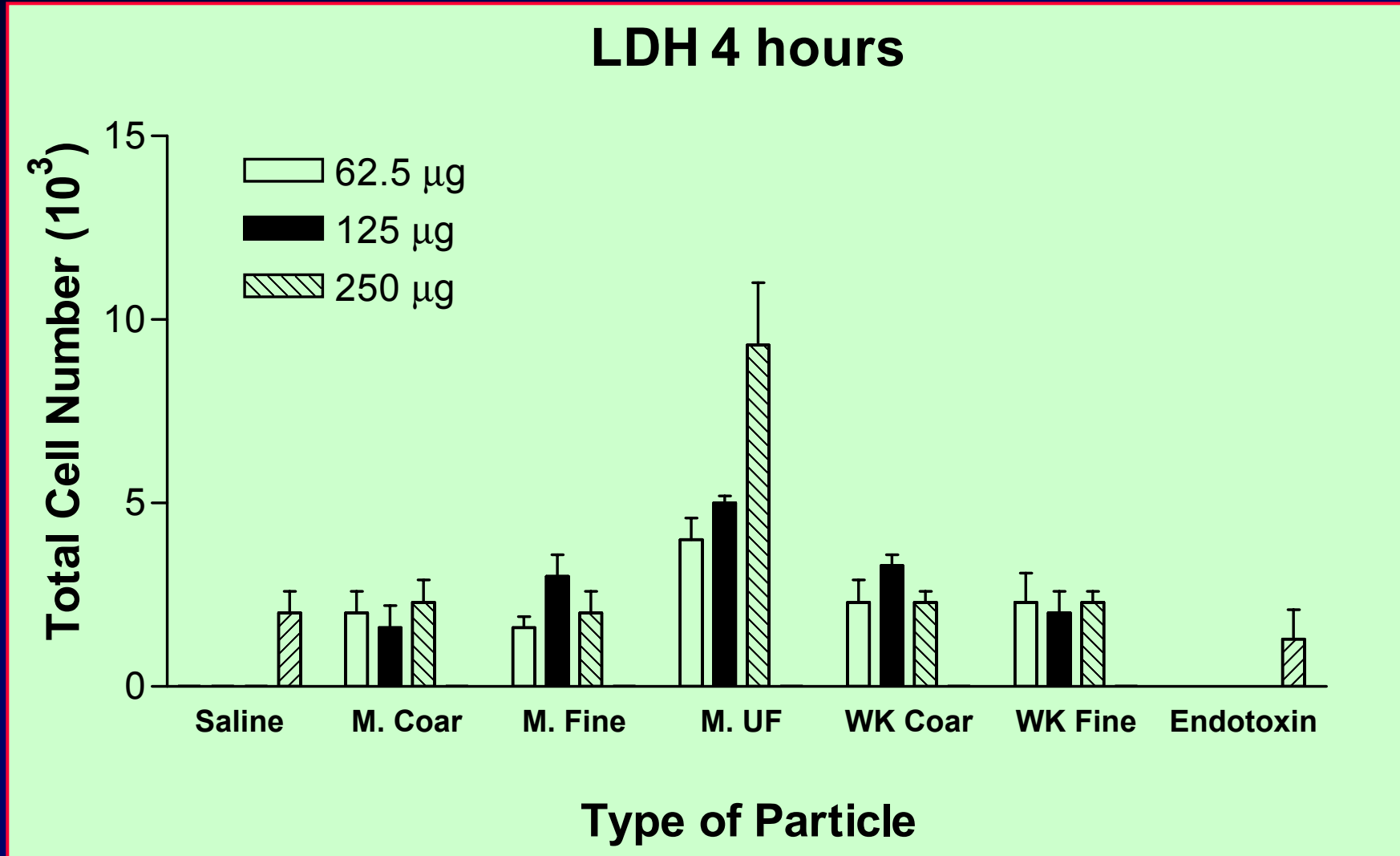
# Effect of coal fly ash instillation on PMN numbers in mouse lungs



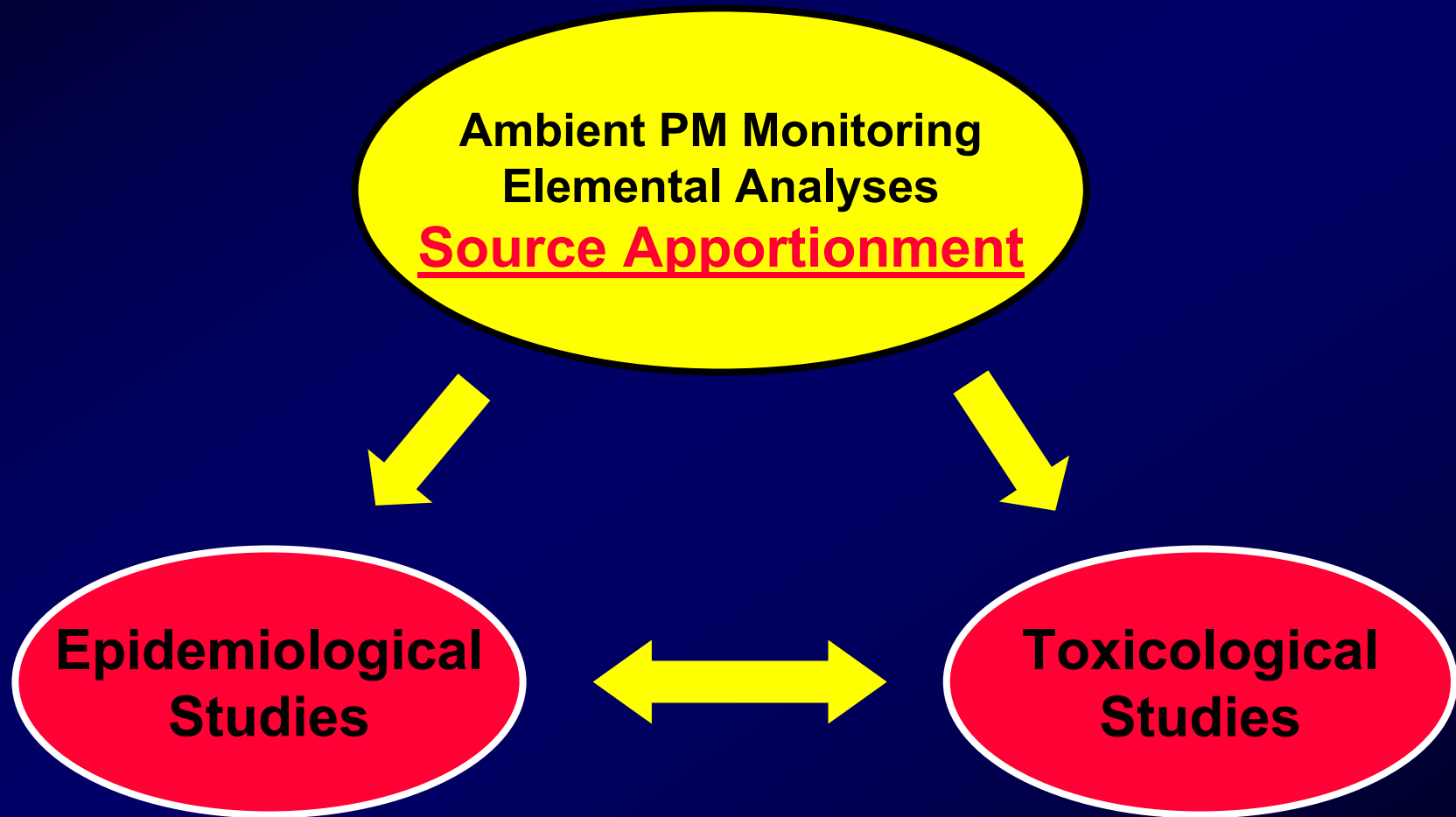
# Effect of coal fly ash instillation on TNF- $\alpha$ levels in mouse lungs



# Effect of coal fly ash incubation on LDH release from rat alveolar macrophages



# Health Effects of Source Specific Particles



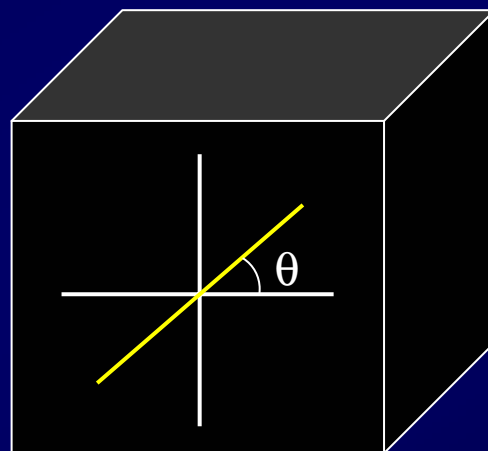
# What are Alternate Approaches?

**Factor Analysis** - Reduces Many Variables to a Small Number of Factors

## Observations

**Chemical Species**

a1	a2	a3	a...	→
b1	b2	b3	b...	→
c1	c2	c3	c...	→
d1	d2	d3	d...	→
e1	e2	e3	e...	→
f1	f2	f3	f...	→
g1	g2	g3	g...	→
h1	h2	h3	h...	→
i1	i2	i3	i...	→
j1	j2	j3	j...	→



“Rotation  
Analysis”

→ **Factor A**

→ **Factor B**

→ **Factor C**

•

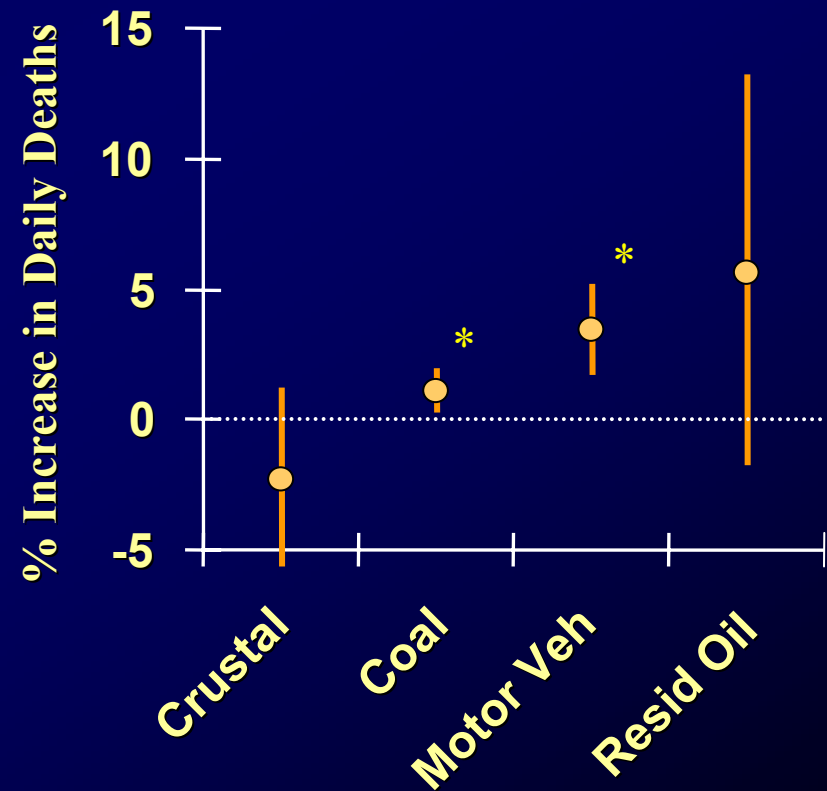
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**Factors explain large  
fraction of data variance**

# Linking Health Effects to Specific Sources

Source-Specific PM<sub>2.5</sub> and Daily Mortality in Six US Cities  
Laden et al., EHP 2000

- ③ PM<sub>2.5</sub> associated with daily mortality in six cities (1980's)
- ③ Factor analysis of elemental composition of PM<sub>2.5</sub> used to estimate source-specific concentrations
- ③ Associations estimated with 4 source classes (10 µg/m<sup>3</sup>)
  - Crustal (Si)
  - Motor Vehicle (Pb)
  - Coal (Se)
  - Residual Oil (V, Mn)



# Conclusions

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- ▶ TOX studies: plausibility, hazard ID, mechanisms
- ▶ High doses often necessary to see effects – more sensitive models, methods, & approaches needed
- ▶ There appears to be strong size and composition dependency of emission PM
- ▶ There is need for data on toxicity of specific sources of air pollution and mixtures of sources
- ▶ Collaboration between epidemiology and toxicology will result in findings of stronger associations of health effects with air pollutants than can be achieved by either discipline alone.

# Future Research

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- **Novel areas:**

- Application of factor analysis (related approaches) may provide a fruitful area for epi & tox research to assess health effects of specific sources of PM - on specific health outcomes (CVD, COPD, pneumonia) – beneficial to regulatory agencies.
- Mixtures studies by combining sources?
- Genomics, proteomics approaches to scope specific effects; may allow high through put analyses.

- **Opportunities for future studies:** Exploit toxicology-epidemiology analogies to define contributing toxicants in the PM complex - specific sources of PM – e.g. speciation sites

# Mortality Scenario: Fatal Arrhythmia (?)

